26. (New) A method of improving angiogenesis in a wound area comprising applying to said wound a bone-derived mixture of proteins which, when subjected to sodium dodecyl sulfate polyacrylamide gel electrophoresis, yields a reduced or non-reduced protein band pattern as identified in Figure 1, said composition including a pharmaceutically acceptable carrier.

REMARKS

Applicants respectfully acknowledge receipt of the Office Action mailed February 11, 2002. In that Office Action, the Examiner (1) rejected claims 1-5 under 35 U.S.C. § 102(b) based on US patent No. 5,393,739; (2) rejected claims 1-8 under 35 U.S.C. § 102(b) based on US patent Nos. 5,459,047 and 5,543,394; (3) rejected claims 1-8 under 35 U.S.C. § 102(e) based on US patent No.6,150,328; (4) rejected claims 9-12 under 35 U.S.C. § 102(b) based on US patent Nos. 5,290,763, 5,563,124, and 5,371,191; (5) rejected claims 13-18, 20 and 23 under 35 U.S.C. § 103(a) based on the '328 and '739 patents and US patent No. 4,950,483; (6) rejected claims 19 and 21 under 35 U.S.C. § 103(a) based on the '328, 739, '483 patents; (7) rejected claim 24 under 35 U.S.C. § 103(a) based on the '328, '739, and '483 patents and US patent No. 5,616,490; (8) rejected claims 9-13 and 16-18 under 35 U.S.C. § 112; and (9) objected to the specification and claims 9-12.

Status of Claims

Claims 1-13 and 16-18 have been amended and new claims 25 and 26 have been added.

Rejection of Claims under 35 U.S.C. § 102(b)

Claims 1-5 stand rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,393,739 ("the '739 patent"). In response, Applicants have amended the claims such that they are now drawn to a method of using the compositions to promote wound healing.

In the Office Action, the Examiner further states that fracture repair and repair of bone damaged by periodontal disease (as described in the '739 patent) are forms of wound healing. In the present application, however, Applicants use of the term "wound healing" is distinct from osteogenesis. See, for example, the Specification at page 5, lines 32-33:

> *"When BP was tested in an animal model to determine if it would be effective in aiding wound closure, it was surprisingly discovered that BP promotes wound*

healing, even though it is a markedly different process than osteogenesis."
(underlining added for emphasis)

Claims 1-8 stand rejected under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,459,047 ("the '047 patent") and U.S. Patent 5,543,394 ("the '394 patent"). Claims 1-5, which have been amended as described above with respect to the '739 patent, now recite a method of promoting wound healing instead of a composition, and are believed to distinguish over the '047 and '394 patents. Although the '047 and '394 patents suggest that BMP-5, BMP-6, and mixtures of BMP proteins, **may** be useful for wound healing, there is no example or specific teaching that those proteins are **actually** capable of promoting effective angiogenesis, efficient collagen deposition and proper epithelialization to heal or close a wound. In Applicants' Specification (e.g., at page 2, line 27 through page 4, line 26; and at page 11, lines 5-8) the unpredictability of this field (i.e., promotion of wound healing) is illustrated by summaries of previous test results with a variety of growth factors. Similar to the amendments to claims 1-5 (above), claims 6-8 have also been amended to recite a method of using the indicated compositions to promote wound healing. Neither the '047 nor the '394 patent teach or suggest treating a wound with the particular composition of claim 6, nor the ribosome-free composition of claim 7. Neither do those references teach or suggest the importance of phosphorylation and glycosylation, as recited in claim 8. For at least these reasons, Applicants submit that claims 1-8 as amended distinguish over the cited references.

In the Office Action dated February 2, 2002, claims 9-12 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,290,763 ("the '763 patent"), U.S. Patent No. 5,563,124 ("the '124 patent") and U.S. Patent No. 5,371,191 ("the '191 patent"). The Examiner points out that purified compositions in pharmaceutically acceptable carriers are taught in each of those references and that Figure 1 of each of those patents is identical to the instant Figure 1. Applicants acknowledge that the osteogenesis studies that are disclosed in the '763, '124 and '191 patents (which are co-owned with the instant application) employed a protein cocktail having the same characteristic SDS-page band pattern of Figure 1. However, those earlier studies do not teach modification of that original protein mixture as described in claims 9-12 (i.e., to remove histones, or ribosomes or to ensure that the proteins are phosphorylated or glycosylated). Neither do the '763, '124 and '191 patents demonstrate that the protein mixture of Figure 1 can function as a wound healing agent. For at least these reasons, claims 9-12 distinguish over the cited references.

Rejection of Claims under 35 U.S.C. § 102(e)

Claims 1-8 further stand rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,150,328 ("the '328 patent"). Even though the '328 patent suggests that purified compositions of BMP-2 and BMP-4 **may** be useful in wound healing and related tissue repair, there is no teaching that either of those proteins is **actually** capable of functioning in that way in a clinical or pre-clinical test. Considering the unpredictability of the art (i.e., promotion of wound healing), as discussed above with respect to the rejection of claims 1-8, without a distinct showing of wound healing activity this reference is at best only an invitation to experiment or to try BMP-2 and BMP-4 in wound healing experiments.

> To be anticipating, a prior art reference must disclose "each and every limitation of the claimed invention[,] ... must be enabling[,] and [must] describe ... [the] claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *Helifix Ltd. v. Blok-lok, Ltd* 208 F.3d 1339-1353 (quoting *In re Paulsen*, 30 F.3d 1475 (Fed. Cir. 1994).

Also, see 1 DELLER'S WALKER ON PATENTS § 60, at 277 (2nd ed. 1964); and *In re O'Farrell* 853 F.2d 894-904 (Fed. Cir. 1988) ("obvious to try" is improper grounds for a §103 rejection.) Applicants respectfully submit that the '328 patent has not enabled the claimed wound healing method of claims 1-8. Accordingly, Applicants believe that claims 1-5 and 6-8 as amended, for the reasons stated above, all distinguish over the '328 patent.

Rejection of Claims under 35 U.S.C. § 103(a)

Claims 13-18, 20 and 23 were rejected in the Office Action dated February 11, 2002 as obvious over the '328 patent and further in view of the '739 patent and U.S. Patent No. 4,950,483 ("the '483 patent"). As stated above, the '328 patent only suggests that the BMP proteins, EGF, FGF and the TGFs **may** be used for wound healing and tissue repair. There are no examples in the '328 patent showing that this is **actually** the case. The '483 patent teaches addition of synergistic amounts of TGF-β and FGF to a sponge composition to promote wound healing, with no idea of including BMPs. The '739 patent teaches bone growth compositions containing certain BMP proteins, TGF-β1 and/or TGF-β2, but there appears to be no demonstration or suggestion of any

tissue or wound healing activity by that particular composition. Since tissue repair or wound healing is a complex process with quite different considerations from those related to osteogenesis (see, e.g., Applicants' Specification at page 2, lines 3-13), one of skill in the art would not be motivated to combine these references as proposed by the Examiner. Even if one were to combine the references, one of skill in the art would not have sufficient basis for expecting that the resulting composition would work as a wound healing agent. Without the teachings of the present disclosure, one of skill in the art would, at best, only be led to try certain BMP-growth factor combinations in a wound healing experiment with no reasonable expectation of success. For at least these reasons, claims 13-18, 20 and 23 are believed to be non-obvious over the cited references.

Claims 19 and 21 stand rejected under 35 U.S.C. § 103(a) as obvious over the '328 patent in view of the '739 and '483 patents, and further in view of U.S. Patent No. 4,950,273 ("the '273 patent"). The Examiner states that the '273 patent teaches use of a hydrogel to deliver certain compositions and that it would be obvious to combine this teaching with the combined teachings of the '328, 739 and '483 patents. In response, Applicants submit that even if these references were combined as suggested by the Examiner, one would still not have the methods of claims 19 and 21 because even including a hydrogel in the composition would not support a reasonable expectation of success for the same reasons discussed above. Accordingly, claims 19 and 21 are believed to be patentable over the combined references.

Claim 24 stands rejected under 35 U.S.C. § 103(a) as being obvious over the '328 patent in view of the '739 and '483 patents, and further in view of U.S. Patent No. 5,616,490 ("the '490 patent"). In the Office Action is it stated that inhibition of TNF-α is taught by the '490 patent as a means to inhibit inflammatory disease, while it is acknowledged that the '490 patent fails to teach inhibition of TNF-α in combination with growth factors to promote wound healing. Even if one would be motivated to combine the wound healing-related patents ('328 and '483) with the '490 patent because inflammation is an early step in wound healing, there would still be insufficient motivation to combine the wound healing references with the osteogenesis reference ('739). Even if these references were combined as suggested by the Examiner, one would still not have the method of claim 24 because, for the reasons discussed above with respect to claims 13-18, 20 and 23, there would be no reasonable expectation of success that such a combination would actually

promote wound healing. Accordingly, claim 24 is also believed to be patentable over the combined references.

Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

Claims 9-13 and 16-18 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In the Office Action, claims 9-12 are considered indefinite for failing to provide antecedent basis for the phrase "the histones." Similarly, claims 10-12 are considered indefinite for failing to provide antecedent basis for the phrase "the ribosomes." In response, claims 9-12 have been amended to provide clearer antecedent basis for "histones" and "ribosomes." Support for the amendments to these claims is found in the specification, for example, at page 7, lines 8-10.

Claims 9-12 are also objected to as being indefinite for referencing "proteins as identified in Figure 1." In response, claims 9 and 11 have been amended to recite "when subjected to sodium dodecyl sulfate polyacrylaminde gel electrophoresis, yields a reduced or non-reduced protein band profile as indicated in Figure 1." Support for the amendments to these claims is found in the specification, for example, at page 7, lines 30-31 and in Figure 1.

Claim 13 is objected to as being indefinite for repeating TGF-β2. In response, the claim has been amended to correct a typographical error by which TGF-β3 was inadvertently omitted. Support for the amendment to this claim is found in the specification, for example, at page 6, line 33.

Claims 16 and 17 are objected to as lacking antecedent basis for "the components." In response, these claims have been amended to recite "said proteins" instead of "the components."

Claim 18 is objected to as referring to "claims 13." In response, the typographical error was corrected such that the claim now recites "claim 13."

Specification

In the Office Action dated February 11, 2002 the Examiner noted the use of certain trademarks in the Specification. Applicants believe that each such trademark has been properly identified by capitalization and the symbol (r), (tm), ® or ™, along with applicable generic terminology.

Claim Objections

Claims 9-12 stand objected to for referring to a figure. In reply, applicants respectfully request permission to refer to Figure 1 in these claims because there is no practical way to define the invention in words, and it is more concise to incorporate Figure 1 by reference in the claims than to duplicate the characteristic SDS gel electrophoresis protein band pattern directly into the claims. The permissibility of incorporation by reference of figures or tables under exceptional circumstances is recognized in 2173.05(s) MPEP and *Ex parte Alfred A. Fressola* 27 U.S.P.Q. 2d 1608 (1993). Claims 9-12 have been amended for clarity and distinctness, as discussed above with respect to the objections under § 112.

New Claims

New claims 25 and 26 have been added to ensure coverage of two specific embodiments to which Applicants are entitled. The subject matter of both of these claims is supported in the original claims and/or specification. For example, in Example 3 at page 12, line 5 through page 14, line 9.

Conclusion

Applicants may have at times referred to claim limitations in shorthand fashion, or may have focused on a particular claim element. This discussion should not be interpreted to mean that the other limitations can be ignored or dismissed. The claims must be viewed as a whole, and each limitation of the claims must be considered when determining the patentability of the claims.

Consideration of the foregoing amendments and remarks, reconsideration of the application and withdrawal of the rejections and objections is respectfully requested. No new matter is introduced by way of the amendments. It is believed that each ground of objection and rejection raised in the Office Action dated February 11, 2002 has been fully addressed. However, if a telephone conference would facilitate the resolution of any issue, the Examiner is invited to telephone the undersigned at (713) 561-6374. If any fee is due as a result of the filing of this paper, please appropriately charge such fee to Sulzer Medica Deposit Account No. 09-0473.

Respectfully submitted,

May 13, 2002
Date

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MARKED-UP VERSION OF THE AMENDMENTS

1. (Amended) A method of promoting wound healing comprising applying to said wound ~~A composition for the treatment of wounds, said~~a composition comprising the growth factors BMP-3 and TGF-β2 in a pharmaceutically acceptable carrier.

2. (Amended) The method of claim 1 wherein the~~The~~ composition ~~of claim 1, further comprising~~ comprises a growth factor selected from the group consisting of BMP-2, BMP-4, BMP-5, BMP-6, and BMP-7.

3. (Amended) The method of claim 1 wherein the~~The~~ composition ~~of claim 2, further comprising~~ comprises a growth factor selected from the group consisting of FGF-1, TGF-β1, and TGF-β3.

4. (Amended) The method of claim 1 ~~The composition of claim 3,~~ wherein the growth factors are derived from a natural source and are at least partially phosphorylated and glycosylated.

5. (Amended) The ~~composition~~ method of claim 1, wherein said composition is free of ~~excluding~~ histone proteins H1c and H1x.

6. (Amended) ~~A composition for the treatment of wounds,~~ The method of claim 1 wherein said composition ~~comprising~~ comprises a mixture of growth factors comprising BMP-2, BMP-3, BMP-6, and TGF-β2 in a pharmaceutically acceptable carrier.

7. (Amended) The method of claim 1 wherein said ~~The~~ composition ~~of claim 6, from which~~is substantially free of ribosomal proteins LORP, Lg, s20, L3, S3a, S4 and L32 ~~have been substantially excluded~~.

8. (Amended) The method of claim 1 wherein said ~~The composition of claim 7, wherein~~ the growth factors are derived from bovine bone and are at least partially phosphorylated and glycosylated.

9. (Amended) A composition for the treatment of wounds, said composition comprising a histone-depleted mixture of proteins comprising a bone-derived protein cocktail which, when subjected to sodium dodecyl sulfate polyacrylaminde gel electrophoresis, yields a reduced or non-reduced protein band profile as ~~identified~~ indicated in Figure 1, said bone-derived protein cocktail having been treated to remove ~~wherein the~~ histone proteins ~~have been excluded from the mixture~~, said ~~mixture being in~~composition including a pharmaceutically acceptable carrier.

10. (Amended) The composition of claim 9, wherein said histone-depleted mixture of proteins has been further treated to remove~~the~~ ribosomal proteins ~~have been excluded therefrom~~.

11. (Amended) A composition for the treatment of wounds, said composition comprising a ribosome-depleted mixture of proteins ~~components~~ comprising a bone-derived protein cocktail which, when subjected to sodium dodecyl sulfate polyacrylaminde gel electrophoresis, yields a reduced or non-reduced protein band profile as ~~identified~~ indicated in Figure 1, ~~wherein the~~said bone-derived protein cocktail having been treated to remove ribosomal proteins ~~have been excluded therefrom~~, said ~~components being in~~composition including a pharmaceutically acceptable carrier.

12. (Amended) The composition of claim 11, wherein said ribosome-depleted mixture of proteins has been further treated to remove ~~the~~ histone proteins ~~have been excluded therefrom~~.

13. (Amended) A composition for the treatment of wounds, said composition comprising a mixture of proteins comprising BMP-2, BMP-3, BMP-4, BMP-5, BMP-6, BMP-7, TGF-β1, TGF-β2, TGF-β23, FGF-1 in a pharmaceutically acceptable carrier.

16. (Amended) The composition of claim 13, wherein ~~the components are~~said proteins have been isolated from a natural source and are at least partially phosphorylated and glycosylated.

17. (Amended) The composition of claim 13, wherein ~~said~~ at least one of ~~the components~~said proteins is a recombinantly produced protein.

18. (Amended) A method of promoting wound healing, said method comprising applying a composition as in claims 13 to a wound.